pending claims after entry of the present amendment is set forth in Appendix 3. A marked-up version of the claims, showing the changes made thereto, is included herein as Appendix 4.

REMARKS

Entry of the above amendments and examination of the application are respectfully requested. After entry of the amendments, claims 1-2 and 4-27 will be pending. Claim 3 has been cancelled, claims 4, 6 and 11-16 have been amended and new claims 24-27 have been added. These amendments are to correct various minor typographical errors in the claims, correct improper claim dependencies, and more distinctly claim the subject matter. Applicant does not believe any new matter has been added to the application by these amendments.

Applicants also submit a substitute Sequence Listing in written and in computer readable form. Pursuant to 37 C.F.R. § 1.821 (f), it is hereby stated that the information recorded in computer readable form is identical to the written Sequence Listing and that applicant is in compliance with 37 C.F.R. § 1.825. The following corrections to the Sequence Listing have been made which are not believed to introduce new matter into the specification as described herein:

SEQ ID NO:1, a rat sequence, was inadvertently referred to as a human sequence in the originally filed Sequence Listing. Applicant does not believe this revision to the Sequence Listing adds new matter to the application for several reasons. Support for SEQ ID NO:1 being a rat sequence may be found on page 17, last paragraph, lines 5-6, of the application as originally filed which reads "The rat cDNA has an open reading frame of 3705 bp." SEQ ID NO:1 is 3705 base pairs long. Additionally, one skilled in the art would immediately recognize the amino acid

sequence encoded by SEQ ID NO:1 is that of the rat by comparing the encoded sequence with the rat and human nephrin amino acid sequences in FIG. 1.

SEQ ID NO:3 has been revised to incorporate amino acid sequences A (Ala) and E (Glu) at its C-terminal end. This is not considered by applicant to include new matter for the following reasons: The nucleotide sequence of exon 24, shown in FIG. 2, encodes the revised SEQ ID NO:3. Additionally, the nucleotide sequence from nucleotides 3145-3165 and 3286-3297 of FIG. 2 encodes the amino acid sequence set forth in SEQ ID NO:4. SEQ ID NO:4 is encoded by the nucleotide sequence set forth in SEQ ID NO:5. SEQ ID NO:4 is further described on page 5, lines 4-7, as overlapping the extra- and intracellular domains of the nephrin or nephrin-like molecules, but lacking the nucleic acid sequence encoding the transmembraneous domain of SEQ ID NO:3. Therefore, in light of FIG. 2 and SEQ ID NO:5, one skilled in the art would be immediately aware of the correct sequence for SEQ ID NO:3 set forth in the Sequence Listing submitted herewith.

Moreover, SEQ ID NO:4 inadvertently included an additional amino acid sequence at positions 8 and 9 (i.e., Ala-Glu) in the original Sequence Listing. This sequence has been removed. Support for such an amendment is found in SEQ ID NO:5 which encodes the amino acid sequence set forth in SEQ ID NO:4. One of skill in the art would immediately recognize upon viewing SEQ ID NO:5 the correct SEQ ID NO:4, which does not include Ala-Glu at positions 8 and 9..

Entry of this amendment and favorable examination of the application are respectfully requested.

Respectfully submitted,

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Date: May 20, 2002

APPENDIX 1

The paragraph in the specification at page 1, lines 6-13, reads as follows:

The present invention is related to soluble nephrin-like protein molecules as well as nucleic acid sequences having a substantial similarity with SEQ ID NO:1 and which encode nephrin-like protein molecules which are substantially homologous with human nephrin (SEQ ID NO:2) but lacking the transmembraneous domain (SEQ ID NO:3) thereof. Said nephrin-like molecules and the nucleic acid sequences encoding them are useful for diagnostic determination, prophylactic and therapeutic treatment of diabetic and other nephropathies, of diabetes mellitus and other inflammatory and neoplastic pancreatic diseases.

The paragraph in the specification at page 3, lines 11-12, reads as follows:

Figure 3 depicts immunoblotting of glomerular lysates with antinephrin antibodies showing distinct reactivity with a 200 kD protein band.

The paragraph in the specification at page 4, lines 1-20, reads as follows:

In the present invention the term **"nucleic acid sequence"** means an isolated nucleic acid sequence encoding nephrin or soluble nephrin-like molecules shared by pancreas and kidney glomerulus and having the **"nucleic acid sequences"** comprise SEQ ID NO:1 or nucleic acid sequences with substantial similarity encoding nephrin-like molecules having an amino acid sequence substantially homologous with SEQ ID NO:2 but lacking the transmembraneous domain GPSGLPLLPVLFALGGLLLLSNASCVGGVLWQRRLRRLAE (SEQ ID NO:3) of nephrin or substantial parts therof. Preferably the nucleic acid should encode a polypeptide having the characteristics described above and at least one contiguous amino acid sequence LPTEPPSGISE (SEQ ID NO:4) surrounding the transmembraneous domain. The overlapping sequence can be longer or shorter than said SEQ ID NO:4 and/or it can in addition to the transmembraneous domain lack one or more, preferably three or more amino acid sequences from the left or right side of the transmembraneous domain. The most important characteristic feature of the nucleotide and/or amino acid sequence of the present invention being the solubility, which provides possibilities to detect the protein from blood, serum and/or urine samples as well as from tissue fluids. In other words the protein is not basement membrane bound. Because the transmembraneous domain is missing and domains from both sides or either side of the transmembraneous domain, i.e. intra- and extracellular domains, are present, the probability of finding such very

specific regions are highest in the vicinity of the missing domain or area.

The paragraph on page 4, lines 28-36, reads as follows:

The isolated nucleic acid sequences of the present invention also include the human nephrin-like molecules which are obtainable as a cDNA of mRNA expressed by human pancreas and kidney glomerulus. Said sequence differs from the mutation form of NPHS1 gene described by Kestilä et al. (1998) and in WO 99/47562 by having at least one amino acid substituted with another amino acid, e. g. a "Leu" in the human locus or position 97 instead of "His" (corresponding to the human locus, i.e. position 75 in the sequence disclosed in the International Patent Application WO 99/47562), an "Ile" in position 273 instead of a "Leu" corresponding to human locus or position 251 in the International Patent Application WO 99/47562).

The paragraph in the specification on page 5, lines 1-25, reads as follows:

The term **"nucleic acid sequence encoding nephrin-like molecules"** means nucleic acid sequences as well as substantially homologous nucleic acid sequences, including genomic DNA, RNA and/or cDNA which comprise at least one contiguous nucleic acid sequence, encoding the amino acid sequence, LPTEPPSGISE (SEQ ID NO:4) overlapping the extra- and intracellular domains of the nephrin or nephrin-like molecules, but lacking the nucleic acid sequence encoding the transmembraneous domain GPSGLPLLPVLFALGGLLLLSNASCVGGVLWQRRLRRLAE (SEQ ID NO:3). As an example of such nucleic acid sequences the contagious sequence CTG CCC ACA GAG CCA CCT TCA GGC ATC TCA GAG (SEQ ID NO:5) deduced from human cDNA can be mentioned. This sequence or its complementary sequence or nucleic acid sequences containing said sequence or parts thereof, e.g. fragments truncated at the 3'-terminal or 5'-terminal end as well as such sequences containing point mutations are especially useful as probes for detecting nucleic acid sequences of the present invention. Specific nucleic acid sequences useful as primers are the sequences for exon 2 comprising 5'-GAC AAA GCC AGA CAG ACG CAG-3' (SEQ ID NO:6) and 5'-AGC TTC CGC (SEQ ID NO:7) as well as other nucleotide sequences constructed from the known amino acid sequence. It is however clear for those skilled in the art that other nucleic acid sequence capable of encoding nephrin-like molecules and useful for their production can be prepared especially when taking in account the codon degeneracy and varying the amount of triplets taken in consideration on either side of the nucleic acid sequence encoding the transmembrane domain. The nucleic acid sequences encoding nephrin-like molecules should not be capable of hybridizing under stringent condition ((Sambrook, J., et al., Molecular Cloning: A Laboratory Manual., Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1989) with sequence

encoding the transmembrane domain of the nephrin or parts thereof.

The paragraph in the specification on page 5, lines 27-32, reads as follows:

The nucleic acid sequences of the present invention should have a substantial similarity with nucleotide sequences which fulfill the prerequisites defined above and have a significant similarity, i.e. a sequence identity of at least 60 %, preferably 70 %, most preferably more than 80 % with a nucleic acid sequence encoding the intra- and extracellular domains, but lacking the region encoding the transmembraneous domain of human nephrin.

The paragraph in the specification at page 6, lines 15-19, reads as follows:

The **"nephrin-like molecules"** are substantially homologous with the amino acid sequence SEQ ID NO:2: but lacking the transmembraneous domain, i.e. at least the amino acid sequence between the amino acid Glu position 1051 and amino acid Lys position 1100 or preferably the amino acid sequences between positions 1056 and 1093 GPSGLPLLPVLFALGGLLLLSNASCVGGVLWQRRLRRLAE (SEQ ID NO:3).

The paragraph in the specification at page 6, lines 21-24, reads as follows:

The term **"substantially homologous"** at amino acid level means that the nephrin-like protein molecules have a significant similarity or identity of at least 80%, preferably 85 %, most preferably more than 90 % with human nephrin (SEQ ID NO:2) but lacks the transmembraneous domain (SEQ ID NO:3).

The paragraph in the specification at page 8, lines 12-23, reads as follows:

Said binding substances can be produced using the intra- and extracellular domains of nephrin or any nephrin-like molecules, their isomers as well as their fragments, derivatives and complexes with the prerequisite that they lack the transmembraneous domain and are capable of acting as **"antigens"**, in other words, antigens include any compositions or materials capable of eliciting an antibody response specific to said nephrin-like molecules. Said binding substances, preferably antibodies are producible by conventional techniques for producing polyclonal antibodies as well as monoclonal antibodies. The methods for preparing monoclonal antibodies include hybridoma techniques. Fragments of antibodies or other binding proteins like specific binding peptides can be developed by phage display techniques and produced by recombinant DNA techniques. All methods are well known by those skilled in the art and described in laboratory handbooks.

The paragraph in the specification at page 14, line 35, to page 15, line 15, reads as follows:

Based on the results obtained and the antibodies available the present inventor developed new methods and test kits for an effective, rapid, and reliable assessment of the status as well as for identifying the phases of disease activity in pancreas and kidneys of human beings. The methods and test kits of the present invention are based on the fact that there is a relation especially between the presence of nephrin-like molecules and autoantibodies against said nephrin-like molecules and susceptibility and the severity of disease activity. Also indicated is the fact that certain nephrin-like molecules alone or in any combination are more specific than others in assessing the disease and that there is some differences in specificity and selectivity, too. Hence, it is advantageous to develop test kits by which a multitude of nephrin-like molecules alone or in any combination could be determined simultaneously, either on the same test strip or on separate test strips. One or more of the binding substances or the fragments of soluble nephrin or nephrin-like molecules can be combined in a test strip or test kit in such a way that one or more of the soluble molecules having the intra- or extracellular domains are combined in such a way that the identification of the transmembrane-free nephrin or nephrin-like molecules is enabled. In preferred embodiments the nephrin-like molecules, shown to be most suitable or effective for a specific diagnostic purpose, were selected for the test kit, either alone or in any

combination.

The paragraph in the specification at page 16, lines 6-16, reads as follows:

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The nucleic acid sequences of the present invention, which have been defined above, as including nucleic acid sequences encoding the intracellular and extracellular domains of SEQ ID NO:2 lacking the transmembraneous domain (SEQ ID NO:3) can be used to produce suitable primers and probes to be applied in *per se* known hybridization techniques and PCR-techniques. Many applicaple and feasible methods and techniques are described in literature, patent publications, laboratory handbooks and can be adapted to the purposes of the present invention. Some test kits for said methods are even commercially available and can be adapted for the purposes of the present invention. The PCR-techniques for amplifying, detecting and/or cloning nucleic acid sequences were first described and patented by Mullis, K.B. et al. for example in the European Patents EP 200 362 and EP 201 184.

The paragraph in the specification at page 16, lines 18-23, reads as follows:

B12

Suitable primers and probes for amplification and/or nucleic hybridization techniques can be found among fragments and/or parts of the nucleic acid sequence encoding nephrin-like molecules having the amino acid sequence SEQ ID NO:2 lacking SEQ ID NO:3, excluding any parts hybridizing with the nucleic acid sequences encoding the transmembraneous domain of nephrin. The nucleic acid sequence used as primers and probes should comprise at least 10 nucleotides complementary to 10, preferably 15, most preferably 20 consecutive nucleotides from the above-defined sequence.

The paragraph in the specification at page 17, lines 25-36, reads as follows:

B13

Despite the increased availability of genetically modified mouse strains, the experimental models in the rat have provided the most widely employed and versatile models to study diabetic and other nephropathies and diabetes mellitus and other inflammatory and neoplastic pancreatic diseases including their pathophysiology and functional genetics. The present inventor has cloned and characterized the rat nephrin cDNA. The rat cDNA has an open reading frame of 3705 bp, and shows 82 % sequence identity to the human nephrin cDNA and shows characteristic rat specific splicing variants. The translated nucleotide sequence has 89 % sequence identity at

B13

the amino acid level. The signal sequence, glycosylation and cystein localization patterns are nearly identical with those of human nephrin. Like the human, the rat nephrin transcript is expressed in a tissue restricted pattern. Thus, preparation of transgenic animals is enabled by the present invention.

APPENDIX 2

Please amend the paragraph on page 1, lines 6-13, as follows:

The present invention is related to soluble nephrin-like protein molecules as well as nucleic acid sequences having a substantial similarity with SEQ ID NO:1[:] and which encode nephrin-like protein molecules which are substantially homologous with human nephrin (SEQ ID NO:2[:]) but lacking the transmembraneous domain (SEQ ID NO:3[3:]) thereof. Said nephrin-like molecules and the nucleic acid sequences encoding them are useful for diagnostic determination, prophylactic and therapeutic treatment of diabetic and other nephropathies, of diabetes mellitus and other inflammatory and neoplastic pancreatic diseases.

Please amend the paragraph in the specification at page 3, lines 11-12, as follows:

Figure 3 depicts immunoblotting of glomerular lysates with antinephrin antibodies showing distinct reactivity with a 200 kD protein band.

Please amend the paragraph in the specification at page 4, lines 1-20, as follows:

In the present invention the term **"nucleic acid sequence"** means an isolated nucleic acid sequence encoding nephrin or soluble nephrin-like molecules shared by pancreas and kidney glomerulus and having the **"nucleic acid sequences"** comprise SEQ ID NO:1: or nucleic acid sequences with substantial similarity encoding nephrin-like molecules having an amino acid sequence substantially homologous with SEQ ID NO:2[:] but lacking the transmembraneous domain GPSGLPLLPVLFALGGLLLLSNASCVGGVLWQRRLRRLAE (SEQ ID NO:3[:]) of nephrin or substantial parts therof. Preferably the nucleic acid should encode a polypeptide having the characteristics described above and at least one [contagious] contiguous amino acid sequence LPTEPPS[GAE]GISE (SEQ ID NO:4[:]) surrounding the transmembraneous domain. The overlapping sequence can be longer or shorter than said SEQ ID NO:4[:] and/or it can in addition to the transmembraneous domain lack one or more, preferably three or more amino acid sequences from the left or right side of the transmembraneous domain. The most important characteristic feature of the nucleotide and/or amino acid sequence of the present invention being

the solubility, which provides possibilities to detect the protein from blood, serum and/or urine samples as well as from tissue fluids. In other words the protein is not basement membrane bound. Because the transmembraneous domain is missing and domains from both sides or either side of the transmembraneous domain, i.e. intra- and extracellular domains, are present, the probability of finding such very specific regions are highest in the vicinity of the missing domain or area.

Please amend the specification at page 4, lines 28-36, to read as follows:

The isolated nucleic acid sequences of the present invention also include the human nephrin-like molecules [encoding nucleic acid sequence SEQ ID NO:1:,] which [is] are obtainable as a cDNA of mRNA expressed by human pancreas and kidney glomerulus. Said sequence differs from the mutation form of NPHS1 gene described by Kestilä et al. (1998) and in WO 99/47562 by having at least one amino acid substituted with another amino acid, e. g. a "Leu" in the human locus or position 97 instead of "His" (corresponding to the human locus, i.e. position 75 in the sequence disclosed in the International Patent Application WO 99/47562), an "Ile" in position 273 instead of a "Leu" corresponding to human locus or position 251 in the International Patent Application WO 99/47562).

Please amend the paragraph in the specification at page 5, lines 1-25, as follows:

The term **"nucleic acid sequence encoding nephrin-like molecules"** means nucleic acid sequences as well as substantially homologous nucleic acid sequences, including genomic DNA, RNA and/or cDNA which comprise at least one [contagious] contiguous nucleic acid sequence, encoding the amino acid sequence, LPTEPPS[AE]GISE (SEQ ID NO:4[:]) overlapping the extra- and intracellular domains of the nephrin or nephrin-like molecules, but lacking the nucleic acid sequence encoding the transmembraneous domain GPSGLPLLPVLFALGGLLLLSNASCVGGVLWQRRLRRLAE (SEQ ID NO:3[:]). As an example of such nucleic acid sequences the contagious sequence CTG CCC ACA GAG CCA CCT TCA GGC ATC TCA GAG (SEQ ID NO:5[:]) deduced from human cDNA can be mentioned. This sequence or its complementary sequence or nucleic acid sequences containing said sequence or parts thereof, e.g. fragments truncated at the 3'-terminal or 5'-terminal end as well as such sequences containing point mutations are especially useful as probes for detecting nucleic acid sequences of the present invention. Specific nucleic

acid sequences useful as primers are the sequences for exon 2 [comprise] comprising 5'-GAC AAA GCC AGA CAG ACG CAG-3' (SEQ ID NO:6[:]) and 5'-AGC TTC CGC (SEQ ID NO:7[:]) as well as other nucleotide sequences constructed from the known amino acid sequence. It is however clear for those skilled in the art that other nucleic acid sequence capable of encoding nephrin-like molecules and useful for their production can be prepared especially when taking in account the codon degeneracy and varying the amount of triplets taken in consideration on either side of the nucleic acid sequence encoding the transmembrane domain. The nucleic acid sequences encoding nephrin-like molecules should not be capable of hybridizing under stringent condition ((Sambrook, J., et al., Molecular Cloning: A Laboratory Manual., Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1989) with sequence encoding the transmembrane domain of the nephrin or parts thereof.

Please amend the paragraph in the specification on page 5, lines 27-32, as follows:

The nucleic acid sequences of the present invention should have a substantial similarity with [the SEQ ID NO:1:. **"Substantial similarity"** means that the] nucleotide sequences which fulfill the prerequisites defined above and have a significant similarity, i.e. a sequence identity of at least 60 %, preferably 70 %, most preferably more than 80 % with [the regions of SEQ ID NO:1:,] a nucleic acid sequence encoding the intra- and extracellular domains, but lacking the region encoding the transmembraneous domain of human nephrin.

Please amend the paragraph in the specification at page 6, lines 15-19, as follows:

The **"nephrin-like molecules"** are substantially homologous with the amino acid sequence SEQ ID NO:2: but lacking the transmembraneous domain, i.e. at least the amino acid sequence between the amino acid Glu position 1051 and amino acid Lys position 1100 or preferably the amino acid sequences between positions 1056 and 1093 GPSGLPLLPVLFALGGLLLLSNASCVGGVLWQRRLRRLAE (SEQ ID NO:3[:]).

Please amend the paragraph in the specification at page 6, lines 21-24, as follows:

The term **"substantially homologous"** at amino acid level means that the nephrin-like protein molecules have a significant similarity or identity of at least 80%, preferably 85 %, most preferably more than 90 % with human nephrin (SEQ ID NO:2[:]) but lacks the transmembraneous domain (SEQ ID NO:3[:]).

Please amend the paragraph in the specification at page 8, lines 12-23, as follows:

Said binding substances can be produced using the intra- and extracellular domains of nephrin or any nephrin-like molecules, their isomers as well as their fragments, derivatives and complexes with the prerequisite that they [are] lack the transmembraneous domain and are capable of acting as **"antigens"**, in other words, antigens include any compositions or materials capable of eliciting an antibody response specific to said nephrin-like molecules. Said binding substances, preferably antibodies are producible by conventional techniques for producing polyclonal antibodies as well as monoclonal antibodies. The methods for preparing monoclonal antibodies include hybridoma techniques. Fragments of antibodies or other binding proteins like specific binding peptides can be developed by phage display techniques and produced by recombinant DNA techniques. All methods are well known by those skilled in the art and described in laboratory handbooks.

Please amend the paragraph in the specification at page 14, line 35, to page 15, line 15, as follows:

Based on the results obtained and the antibodies available the present inventor developed new methods and test kits for an effective, rapid, and reliable assessment of the status [and tissue destruction status] as well as [to identify] <u>for identifying</u> the phases of disease activity in pancreas and kidneys of human beings. The methods and test kits of the present invention are based on the fact that there is a relation especially between the presence of nephrin-like molecules and autoantibodies against said nephrin-like molecules and susceptibility and the severity of disease activity. Also indicated is the fact that certain nephrin-like molecules alone or in any combination are more specific than others in assessing the disease and that there is some differences in specificity and selectivity, too. Hence, it is advantageous to develop test kits by which a multitude of nephrin-like molecules alone or in any combination could be determined simultaneously, either on the same test strip or on separate test strips.

One or more of the binding substances or the fragments of soluble nephrin or nephrin-like molecules can be combined in a test strip or test kit in such a way that one or more of the soluble molecules having the intra- or extracellular domains are combined in such a way that the identification of the transmembrane-free nephrin or nephrin-like molecules is enabled. In preferred embodiments the nephrin-like molecules, shown to be most suitable or effective for a specific diagnostic purpose, were selected for the test kit, either alone or in any combination.

Please amend the paragraph in the specification at page 16, lines 6-16, as follows:

The nucleic acid sequences of the present invention, which have been defined above, as including nucleic acid sequences encoding the intracellular and extracellular domains of [SEQ ID NO:1: or alternatively defined as] SEQ ID [NO:1:] NO:2 lacking the transmembraneous domain (SEQ ID NO:3[:]) can be used to produce suitable primers and probes to be applied in *per se* known hybridization techniques and PCR-techniques. Many applicaple and feasible methods and techniques are described in literature, patent publications, laboratory handbooks and can be adapted to the purposes of the present invention. Some test kits for said methods are even commercially available and can be adapted for the purposes of the present invention. The PCR-techniques for amplifying, detecting and/or cloning nucleic acid sequences were first described and patented by Mullis, K.B. et al. for example in the European Patents EP 200 362 and EP 201 184.

Please amend the paragraph in the specification at page 16, lines 18-23, as follows:

Suitable primers and probes for amplification and/or nucleic hybridization techniques can be found among fragments and/or parts of the nucleic acid sequence [SEQ ID NO:1:,] encoding nephrin-like molecules having the amino acid sequence SEQ ID NO:2 lacking SEQ ID NO:3, excluding any parts hybridizing with the nucleic acid sequences encoding the transmembraneous domain of nephrin. The nucleic acid sequence used as primers and probes should comprise at least 10 nucleotides complementary to 10, preferably 15, most preferably 20 consecutive nucleotides from the above-defined sequence.

Please amend the paragraph at page 17, lines 25-36, as follows:

Despite the increased availability of genetically modified mouse strains,

the experimental models in the rat have provided the most widely employed and versatile models to study diabetic and other nephropathies and diabetes mellitus and other inflammatory and neoplastic pancreatic diseases including their pathophysiology and functional genetics. The present inventor has cloned and characterized the rat nephrin cDNA. The rat cDNA has an open reading frame of 3705 bp, and shows 82 % sequence identity to the human nephrin cDNA and shows characteristic rat specific splicing variants. The translated nucleotide sequence has 89 % sequence identity at the amino acid level. The signal sequence, glycosylation and cystein localization patterns are nearly identical with those of human nephrin. Like the human, the rat nephrin transcript is expressed in a tissue restricted pattern. Thus, preparation of transgenic animals [are] <u>is</u> enabled by the present invention.

APPENDIX 3

1. An isolated nucleic acid sequence encoding soluble nephrin or soluble nephrin-like molecules shared by pancreas and kidney glomerulus, comprising the nucleic acid sequence set forth in SEQ ID NO:1 or nucleic acid sequences having substantial similarity thereto and encoding nephrin-like molecules having the properties and functions characteristic of nephrin-like molecules, said nephrin-like molecules having an amino acid sequence substantially homologous with the amino acid sequence set forth in SEQ ID NO:2 lacking the amino acid sequence encoding the transmembraneous domain set forth in SEQ ID NO:3 of nephrin.

2. The isolated nucleic acid sequence according to claim 1, wherein said amino acid sequence set forth in SEQ ID NO:2 has intracellular domains and extracellular domains, said nephrin-like molecules further comprising at least one contiguous amino acid sequence SEQ ID NO:4, said amino acid sequence set forth in SEQ ID NO:4 having intracellular and extracellular domains of SEQ ID NO:2.

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4. (Twice Amended) Soluble nephrin-like molecules shared by pancreas and kidney glomerulus, comprising polypeptides or derivatives thereof having the properties and functions characteristic of nephrin-like molecules and having an amino acid sequence substantially homologous with the amino acid sequence set forth in SEQ ID NO:2 lacking the transmembraneous domain set forth in SEQ ID NO:3 of nephrin.

5. The soluble nephrin-like molecules according to claim 4, wherein said molecules further comprise at least one contiguous amino acid sequence substantially homologous to the amino acid sequence set forth in SEQ ID NO:4.

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6. (Amended) A binding substance, comprising an antibody which is capable of specifically recognizing and binding to a portion of an amino acid sequence overlapping an intracellular and extracellular domain of the soluble nephrin-like molecules according to claim 4 or to a portion of an amino acid sequence

overlapping an intracellular and extracellular domain of the nucleic acid sequences encoding said soluble nephrin-like molecules.

11. (Twice Amended) A method for diagnosing whether a subject suffers from nephropathies, inflammatory diseases, or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising soluble nephrin-like molecules according to claim 4; and
(c) recording the absence or presence of a reaction of said soluble nephrin-like molecules when contacted with the sample.

12. (Twice Amended) A method for evaluating the efficacy of treatment modalities in subjects suffering from nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising soluble nephrin-like molecules according to claim 4; and
(c) recording the absence or presence of a reaction of said soluble nephrin-like molecules when contacted with the sample.

13. (Twice Amended) A method for screening for the susceptibility of a population to nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising soluble nephrin-like molecules according to claim 4; and

(c) recording the absence or presence of a reaction of said soluble nephrin-like molecules and the autoantibodies present in the sample.

B/10 cont'd

14. (Twice Amended) A method for diagnosing whether a subject suffers from nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising a binding substance specifically recognizing and binding to a soluble nephrin-like molecule according to claim 4; and
(c) recording the absence or presence of a reaction when said binding substance is contacted with the sample.

15. (Twice Amended) A method for evaluating the efficacy of treatment modalities in subjects suffering from nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising a binding substance specifically recognizing soluble nephrin-like molecules according to claim 4; and
(c) recording the absence or presence of a reaction when contacting the binding substance with the sample.

16. (Twice Amended) A method for screening the susceptibility of a population to nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;

(b) contacting said sample with a reagent comprising a binding substance specifically recognizing a soluble nephrin-like molecule according to claim 4; and
(c) recording the absence or presence of a reaction when contacting said binding substance with the sample.

17. The method according to claim 11, wherein said nephropathies comprise diabetic nephropathies and said inflammatory diseases comprise diabetes mellitus.

18. The method according to claim 12, wherein said nephropathies comprise diabetic nephropathies and said inflammatory diseases comprise diabetes mellitus.

19. The method according to claim 13, wherein said nephropathies comprise diabetic nephropathies and said inflammatory diseases comprise diabetes mellitus.

20. The method according to claim 14, wherein said nephropathies comprise diabetic nephropathies and said inflammatory diseases comprise diabetes mellitus.

21. The method according to claim 15, wherein said nephropathies comprise diabetic nephropathies and said inflammatory diseases comprise diabetes mellitus.

22. The method according to claim 16, wherein said nephropathies comprise diabetic nephropathies and said inflammatory diseases comprise diabetes mellitus.

23. A method for treating a patient with a nephropathy, an inflammatory disease or a neoplastic pancreatic disease, comprising administering to said patient a nucleic acid sequence according to claim 1.

24. (New) An isolated nucleic acid sequence encoding a soluble nephrin or soluble nephrin-like molecules shared by pancreas and kidney glomerulus, comprising the continuous nucleic acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7 or nucleic acid sequences having substantial similarity thereto and encoding nephrin-like molecules or derivatives thereof, having the properties and functions characteristic of nephrin-like molecules, said nephrin-like molecules having an amino

acid sequence substantially homologous with the amino acid sequence set forth in SEQ ID NO:2 lacking the transmembraneous domain set forth in SEQ ID NO:3 of nephrin.

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25. (New) The isolated nucleic acid sequence according to claim 24, further comprising at least one contiguous amino acid sequence set forth in SEQ ID NO:4 having intracellular and extracellular domains of SEQ ID NO:2 or variations thereof.

26. (New) The isolated nucleic acid sequence according to claim 24, wherein said nucleic acid sequence further comprises a continuous nucleotide sequence set forth in SEQ ID NO:5.

27. (New) The isolated nucleic acid sequence according to claim 25, wherein said nucleic acid sequence further comprises a continuous nucleotide sequence set forth in SEQ ID NO:5.

APPENDIX 4

Please cancel claim 3, and amend claims 4, 6 and 11-16 as follows:

B14

4. (Twice Amended) Soluble nephrin-like molecules shared by pancreas and kidney glomerulus, comprising polypeptides or derivatives thereof having the properties and functions characteristic of nephrin-like molecules and having an amino acid sequence substantially homologous with the amino acid sequence set forth in SEQ ID NO:2 lacking the transmembraneous domain set forth in SEQ ID NO:3[:] of nephrin.

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6. (Amended) A binding substance, comprising an antibody which is capable of specifically recognizing and binding to a portion of an amino acid sequence overlapping an intracellular and extracellular domain of the soluble nephrin-like molecules according to claim[s] 4 [or 5] or to a portion of an amino acid sequence overlapping an intracellular and extracellular domain of the nucleic acid sequences encoding said soluble nephrin-like molecules.

11. (Twice Amended) A method for diagnosing whether a subject suffers from nephropathies, inflammatory diseases, or neoplastic pancreatic diseases, said method comprising the steps of:

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(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising soluble nephrin-like molecules according to claim [3] 4; and
(c) recording the absence or presence of a reaction of said soluble nephrin-like molecules when contacted with the sample.

12. (Twice Amended) A method for evaluating the efficacy of treatment modalities in subjects suffering from nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising soluble nephrin-like molecules according to claim [3] 4; and
(c) recording the absence or presence of a reaction of said soluble nephrin-like molecules when contacted with the sample.

B16 cont'd

13. (Twice Amended) A method for screening for the susceptibility of a population to nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising soluble nephrin-like molecules according to claim [3] 4; and
(c) recording the absence or presence of a reaction of said soluble nephrin-like molecules and the autoantibodies present in the sample.

14. (Twice Amended) A method for diagnosing whether a subject suffers from nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising a binding substance specifically recognizing and binding to a soluble nephrin-like molecule according to claim [3] 4; and
(c) recording the absence or presence of a reaction when said binding substance is contacted with the sample.

15. (Twice Amended) A method for evaluating the efficacy of treatment modalities in subjects suffering from nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

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(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising a binding substance specifically recognizing soluble nephrin-like molecules according to claim [3] 4; and
(c) recording the absence or presence of a reaction when contacting the binding substance with the sample.

16. (Twice Amended) A method for screening the susceptibility of a population to nephropathies, inflammatory diseases or neoplastic pancreatic diseases, said method comprising the steps of:

(a) obtaining a blood or urine sample from a subject suspected of suffering from said diseases or being treated for said diseases;
(b) contacting said sample with a reagent comprising a binding substance specifically recognizing a soluble nephrin-like molecule according to claim [3] 4; and
(c) recording the absence or presence of a reaction when contacting said binding substance with the sample.

Please enter new claims 24-27 as follows:

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24. (New) An isolated nucleic acid sequence encoding a soluble nephrin or soluble nephrin-like molecules shared by pancreas and kidney glomerulus, comprising the continuous nucleic acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7 or nucleic acid sequences having substantial similarity thereto and encoding nephrin-like molecules or derivatives thereof, having the properties and functions characteristic of nephrin-like molecules, said nephrin-like molecules having an amino acid sequence substantially homologous with the amino acid sequence set forth in SEQ ID NO:2 lacking the transmembraneous domain set forth in SEQ ID NO:3 of nephrin.

25. (New) The isolated nucleic acid sequence according to claim 24, further comprising at least one contiguous amino acid sequence set forth in SEQ ID NO:4 having intracellular and extracellular domains of SEQ ID NO:2 or variations thereof.

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26. (New) The isolated nucleic acid sequence according to claim 24, wherein said nucleic acid sequence further comprises a continuous nucleotide sequence set forth in SEQ ID NO:5.

27. (New) The isolated nucleic acid sequence according to claim 25, wherein said nucleic acid sequence further comprises a continuous nucleotide sequence set forth in SEQ ID NO:5.